Membranous Nephropathy:
An update for 2015

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Disclosures: Pietro Canetta

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- Consulting: None

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Membranous Nephropathy: Overview

• **Incidence:** 1.2/100,000/yr worldwide, 3.4/100,000 in Northern Italy
  – 70-80% “Idiopathic”
  – 20-30% Secondary
• Most common primary glomerular disease in **older adults** (>60 yr)
• Most common cause of **nephrotic syndrome** in nondiabetic adults
  – More common in **whites** & **asians** than **blacks**
  – Male:Female **2:1 ratio**
• Causes at least 0.7% of cases of ESRD (USRDS)

• **Pathogenesis:** subepithelial antigen-antibody **immune-complex** deposition
  – Diffuse granular **IgG** and **complement** deposition along GBM
  – Different isotypes depending on etiology
  – Can also have mesangial immune complex deposition (more typical of secondary forms)
Secondary Membranous

• **Causes**
  – **Autoimmunity**: Lupus (Class V)
  – **Alloimmunity**: Allograft rejection, GVHD
  – **Infections**: Hepatitis B, syphilis (?HCV)
  – **Malignancy**: esp. solid tumors
  – **Medications**: gold, mercury, penicillamine

• **Diagnostic clues**
  – Systemic disease
  – Demographics
    • Children
    • African ancestry
  – Histology
    • Mesangial or subendothelial deposits
    • Tubuloreticular inclusions
    • Non-IgG4 immunoglobulins
    • TBM staining for IgG by IF
    • **Absence of PLA2R** staining
Periodic acid–Schiff
Methenamine silver
Primary/Idiopathic Membranous Membranous

We can see the antibodies....
So what are the antigens?
M-Type Phospholipase A₂ Receptor as Target Antigen in Idiopathic Membranous Nephropathy

Laurence H. Beck, Jr., M.D., Ph.D., Ramon G.B. Bonegio, M.D., Gérard Lambeau, Ph.D., David M. Beck, B.A., David W. Powell, Ph.D., Timothy D. Cummins, M.S., Jon B. Klein, M.D., Ph.D., and David J. Salant, M.D.
Phospholipase A2 Receptor

- 185-kD glycoprotein present on normal podocytes
- Found in immune deposits of patients with idiopathic MN
- PLA2R and IgG4 co-localize on biopsy specimens from pts with idiopathic MN in a typical granular pattern
- ~70-80% of patients with idiopathic, but not secondary, MN have antibodies against PLA$_2$R

Beck et al., NEJM, July 2, 2009
Rees & Kain, Nature Reviews Nephrology 5, 617-618 (November 2009)
Anti-PLA$_2$R is sensitive & specific for Idiopathic MN


-OR-
Could they have two separate diseases?

Qin et al., JASN 2012: 3/10 patients with +anti-PLA2R and “tumor-associated MN” did not improve after tumor resection
Anti-PLA$_2$R by biopsy vs. serum

Malignancy risk in membranous aPLA$_2$R positive vs. aPLA$_2$R negative

Malignancy occurrence:
aPLA2R negative: 10/27 (37%), sooner
aPLA2R positive: 6/64 (9%), later
Genetics independently confirm association of PLA_2R with IMN

Risk HLA-DQA1 and PLA_2R1 Alleles in Idiopathic Membranous Nephropathy

GWAS of idiopathic MN

Genetics independently confirm association of PLA$_2$R with iMN

<table>
<thead>
<tr>
<th>Table 3. Odds Ratios for Idiopathic Membranous Nephropathy, According to Single-Nucleotide Polymorphism (SNP) and Genotype Combinations.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNP rs2187668 (HLA-DQA1)</strong></td>
</tr>
<tr>
<td>G G</td>
</tr>
<tr>
<td><strong>GG</strong></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td><strong>GA</strong></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td><strong>AA</strong></td>
</tr>
<tr>
<td>No. of cases/total no. of subjects</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
</tr>
</tbody>
</table>

Can Anti-PLA$_2$R-ab testing improve our ability to prognosticate in MN?

- **Natural History** is variable ("Rule of thirds")
  - 1/3 = Spontaneous remission
  - 1/3 = Persistent subnephrotic proteinuria
  - 1/3 = Persistent nephrotic syndrome, progressive CKD
    - Renal survival at 10 y: 65%-85%
    - Renal survival at 15 y: 60%

### Traditional risk factors for progression:
- Older Age
- Male Sex
- Reduced GFR
- Interstitial fibrosis on biopsy
- Heavy proteinuria, especially if persists

### Risk factors for spont. remission:
- Baseline serum creatinine (mg/dl), HR 0.40 (0.19 to 0.85)
- Baseline proteinuria (g/24h), HR 0.85 (0.77 to 0.94)
- Proteinuria decrease >50% in the 1st year, HR 12.6 (5.2 to 30.5)
- ACEI/ARB treatment, HR 2.36 (1.09 to 5.12)

Proteinuria over time in
Spontaneous Remission

- N = 328 with nephrotic syndrome & MN
- 32% experienced spontaneous remission
  - ½ Partial remission by mean $15 \pm 11$ mos
    (range 1-66 mos)
  - ½ Complete remission by mean $39 \pm 25$ mos
    (range 4-120 mos)
Patients with high-titer aPLA$_2$R are unlikely to undergo spontaneous remission

<table>
<thead>
<tr>
<th>Outcome</th>
<th>aPLA$_2$R titer, by tertile</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low 41–175 U/ml (n=26)</td>
<td>Middle 176–610 U/ml (n=26)</td>
<td>High &gt;610 U/ml (n=27)</td>
<td>P Value</td>
</tr>
<tr>
<td>Partial remission</td>
<td>11 (42%)</td>
<td>8 (31%)</td>
<td>11 (41%)</td>
<td>NS</td>
</tr>
<tr>
<td>Complete remission</td>
<td>7 (27%)</td>
<td>9 (35%)</td>
<td>8 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (4%)</td>
<td>3 (12%)</td>
<td>5 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>7 (27%)</td>
<td>6 (23%)</td>
<td>3 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Spontaneous remission*</td>
<td>10 (38%)</td>
<td>8 (31%)</td>
<td>1 (4%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*No treatment with immunosuppressive agents

Hofstra et al., JASN, Oct 2012
None of the patients with +PLA2R antibodies at the end of therapy had a persistent remission.
Survival analysis by tertile of aPLA$_2$R Antibody level

Outcome: 
≥25% rise in sCreat from baseline  
-AND-  
sCreat ≥1.3 mg/dl

![Graph showing survival analysis by tertile of aPLA$_2$R Antibody level](image)

- **High**
  - P (high vs. medium) = 0.19
  - P (high vs. low) < 0.001
  - 3.7 g/24hr

- **Medium**
  - P (medium vs. low) = 0.09
  - 2.5 g/24hr

- **Low**
  - 1.4 g/24hr

| N (high) | 39 | 32 | 22 | 14 | 8 | 6 | 1 |
| N (medium) | 39 | 33 | 23 | 19 | 13 | 9 | 3 |
| N (low) | 40 | 36 | 28 | 26 | 20 | 9 | 4 |

Hoxha E et al. CJASN 2014;9:1883-1890
Can Anti-PLA$_2$R-antibody testing help direct management in MN?

- Assessing remission status?
- Assessing treatment response?
- Assessing need for ongoing or added immunosuppression?
Anti-PLA$_2$R level correlates with disease activity in idiopathic MC

**AntiPLA2R and proteinuria**

- Graph showing the correlation between anti-PLA$_2$R levels and proteinuria.
- The correlation coefficient $r = 0.75$ and $p < 0.01$.

**AntiPLA2R and Remission status**

- Graph showing the anti-PLA$_2$R levels during different remission statuses:
  - Nephrotic
  - Remission
  - Relapse

Hofstra J M et al. CJASN 2011;6:1286-1291
Disappearance of anti-PLA$_2$R precedes that of proteinuria

Beck L H et al. JASN 2011;22:1543-1550
Disappearance of anti-PLA$_2$R precedes that of proteinuria

Hoxha E et al. JASN 2014;25:1357-1366
Time-course of anti-PLA$_2$R antibodies and proteinuria
Suggestions for practical use of anti-PLA₂R titers

• If possible, every membranous nephropathy patient should have anti-PLA2R assessed by biopsy and serum
• In aPLA2R-negative patients, look aggressively for secondary causes (but still idiopathic in 20-30%)
• For patients who are aPLA2R positive on biopsy,
  – Absence of serum aPLA2R may suggest impending remission
  – High-titer serum aPLA2R may suggest low likelihood of remission
• Assessing aPLA2R at the end of immunosuppressive treatment may be useful in assessing likelihood of maintaining remission
• Prospective studies using treatment algorithm based on anti-PLA2R level are necessary for proof of concept
Commercial anti-PLA$_2$R Ab testing

- **List of resources:** [www.euroimmun.us/recent-news/pla2r-testing-locations](http://www.euroimmun.us/recent-news/pla2r-testing-locations)

- **Cincinnati Children’s Hospital**
  - **Nephrology Clinical Laboratory**
  - Tel: 513-636-4530
  - Email: nephclinicallab@cchmc.org
  - Contact: Thelma Kathman
  - Tel: 513-636-9428

- **Massachusetts General Hospital**
  - Contact: A. Bernard Collins
  - Tel: 617-726-8444

- **Nephropath**
  - Contact: Dawn Steppach
  - Tel: 501-604-2695
  - (Charge $120 if insurance doesn’t cover)
What about anti-PLA$_2$R negative “idiopathic” MN?

- Need more antigens.....
THSD7A was identified as the culprit antigen in 10% (15/154) of cases of anti-PLA2R1-negative idiopathic MN (at least 3 provided by CUMC!)
Antigens identified in human membranous nephropathy

- **1959**: Active Heymann nephritis model
- **1973**: Passive Heymann nephritis model
- **1980s**: Megalin identified as Heymann antigen in rats

<table>
<thead>
<tr>
<th>Year</th>
<th>Antigen</th>
<th>Model</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Neutral endopeptidase</td>
<td>Alloimmune MN, neonatal</td>
<td>Debiec et al., NEJM</td>
</tr>
<tr>
<td>2009</td>
<td>PLA2R1</td>
<td>Idiopathic MN</td>
<td>Beck et al., NEJM</td>
</tr>
<tr>
<td>2011</td>
<td>Cationic bovine serum albumin</td>
<td>Early childhood MN, planted antigens</td>
<td>Debiec et al., NEJM</td>
</tr>
<tr>
<td>2014</td>
<td>Recombinant human arylsulfatase B (treatment for Pompe disease)</td>
<td>Alloimmune MN</td>
<td>Debiec et al., NEJM</td>
</tr>
<tr>
<td>2014</td>
<td>Thrombospondin Type-1 Domain-Containing 7A</td>
<td>Idiopathic MN, PLA2R1-negative</td>
<td>Tomas et al., NEJM</td>
</tr>
</tbody>
</table>
**Mechanisms of subepithelial immune deposit formation**

**PLA2R1**  
**THSD7A**  
**Neutral endopeptidase**

**Cationic BSA**  
**Cationic histones? (SLE)**  
**Tumor antigens?**  
**HBV antigens?**

*No human evidence yet*

Beck & Salant, J Clin Invest, 2014;124(6)
Therapy of MN:
KDIGO GN Guidelines 2012

- **Guideline 7.2: When to immunosuppress:**
  - Treat only in nephrotic syndrome AND either:
    - Urinary protein persistently $>4 \text{ g/day}$ and $>50\%$ of the baseline x6 mos observation *(1B)*
    - **severe,** disabling, life-threatening *symptoms* of nephrotic syndrome *(1C)*
    - Creatinine rise $>30\%$ within 6-12 months from diagnosis but eGFR still $>25-30 \text{ ml/min/1.73 m}^2$ *(2C)*

- **Guideline 7.3: Initial therapy:**
  - 6-month course of alternating monthly cycles of **oral and i.v. corticosteroids,** and **oral alkylating agents** *(1B).*
    - Monitor x6 months post-therapy before considering treatment failure *(1C)*

- **Guideline 7.4: Alternative initial regimen:**
  - cyclosporine or tacrolimus x at least 6 months *(1C)*

- **Guideline 7.5: DON’T start with:**
  - corticosteroid or MMF **monotherapy** *(1B/1C)*

- **Guideline 7.6: Resistant membranous:**
  - If failed steroids/alkylators $\rightarrow$ try calcineurin inhibitor, and vice versa *(2C)*
Remission and Relapse after steroids and oral cyclophosphamide

**Remission**
- Partial and complete remissions
- 92% at 5yrs

**Relapse**
- Complete remissions
- 36% at 5yrs

28% at 5yrs
Calcineurin inhibitors for MN as 1st line therapy: two RCTs

**Cyclosporine**
- Pred + Cyclosporine (CsA) vs. Pred + Placebo x 26wks
- **Partial/complete remissions:**
  - At 26 wks: CsA 75% vs. placebo 22% (P<0.001)
  - At 78 wks: CsA 39% vs. placebo 13% (P=0.007)

**Tacrolimus**
- Tacrolimus vs. control x 12 mos with 6 mo. taper
- **Remission:** 94 % vs. 35% at 18 mos

Cattran D et al., Kidney Int 2001
Howman et al, UK Randomized Controlled Trial

Lancet, 2013

- Pred/Chlorambucil group had lower risk of 20% decline in creat clearance and greater fall in proteinuria compared to other groups.

- No difference between supportive care and ciclosporin for primary end point or proteinuria.
Cancer Risk after Cyclophosphamide for Idiopathic MN patients

- N=272, mean 51 yo, 70% male, median follow-up 6.0 yrs (IQR 3.6-9.5 yrs)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incidence Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted</strong></td>
<td>4.6</td>
<td>1.5 to 18.8</td>
</tr>
<tr>
<td><strong>Univariate-adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>3.3</td>
<td>1.0 to 10.6</td>
</tr>
<tr>
<td>Men</td>
<td>3.3</td>
<td>1.1 to 10.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>5.8</td>
<td>1.6 to 20.8</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>4.2</td>
<td>1.3 to 13.4</td>
</tr>
<tr>
<td>Family history of malignancy</td>
<td>7.1</td>
<td>1.6 to 32.0</td>
</tr>
<tr>
<td>CKD stage</td>
<td>5.0</td>
<td>1.5 to 18.8</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>4.3</td>
<td>1.3 to 14.1</td>
</tr>
<tr>
<td><strong>Age- and sex-adjusted</strong></td>
<td><strong>3.2</strong></td>
<td><strong>1.0 to 9.5</strong></td>
</tr>
</tbody>
</table>

For the average patient, this translates into an increase in annual risk from ~0.3% to 1.0%.

Van den Brand JA et al., CJASN, Jun 2014
**IMGN TREATMENT ALGORITHM**

**PLA2R Ab neg or low-range**
- ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Continue to monitor proteinuria and renal function

**PLA2R Ab mid-range**
- ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Observe for 6 months
- Persistent nephrotic range proteinuria**
- Cytotoxic/steroids**
- Cyclosporine**

**PLA2R Ab high-range**
- ACEI ± ARB, dietary protein restriction, Maintain BP ≤ 125/75 mm Hg, Observe for ≤ 6 months*
- Persistent heavy proteinuria and/or decreasing renal function**
- Cyclosporine**
- Cytotoxic/steroids**

*Decreasing function or complication: start treatment early

**Introduction of risk reduction strategies
Beyond KDIGO...

- >60-70% of patients will respond to initial therapy
- Of responders, 25-40% will relapse
- So what else is there?
Rituximab

• Mostly uncontrolled case series or pilot studies
  – *CJASN* 2009: Systematic review on rituximab for MN found 69 patients reported in literature → 50 from single Italian center and 15 from Mayo Clinic

• **MENTOR trial**: ongoing RCT (NCT01180036) comparing rituximab vs. cyclosporine as initial therapy for MN, planned enrollment n=126, results available ?2017
Rituximab: uncontrolled case series

- **N=100**
  - 68 as 1st line therapy
  - 32 as 2nd line therapy

- Partial+Complete remissions = 65/100
- Complete remissions = 27/100
- Median time to remission 7.1 months (IQR 3.2-12.0 months)

- Median total followup 29 months
- 18/65 relapsed
- 11/18 went back in remission (PR+CR) after more rituximab
Rituximab: uncontrolled case series

- N=100
  - 68 as 1st line therapy
  - 32 as 2nd line therapy
- Partial+Complete remissions = 65/100
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- Median total follow-up 29 months
- 18/65 relapsed
- 11/18 went back in remission (PR+CR) after more rituximab

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Overall (n=100)</th>
<th>Complete Remission (n=27)</th>
<th>Partial Remission (n=38)</th>
<th>No remission (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2</td>
<td>1.0*</td>
<td>1.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Proteinuria (g/24h)</td>
<td>9.1</td>
<td>5.8*</td>
<td>8.2</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Ruggenenti P et al. JASN 2012;23:1416-1425
ACTH vs. Prednisone/Cytotoxics

- Proteinuria reduction initially described by Berg and Arnadottir, *NDT* 2004, while studying hyperlipidemia in nephrotic syndrome
- RCT of 32 patients with *treatment-naive* idiopathic MN compared Pred/cytotoxics vs. ACTH with equivalent outcomes

**GROUP A**
Methylpred/Cyclophosphamide  
* x6 months

**GROUP B**
Synthetic ACTH  
* x12 months
ACTH for nephrotic syndrome at CUMC: 11 subjects with MN

9 patients with remission had failed >2 prior immunosuppressive regimens

ACTH in 20 MN patients: Dose-finding study

- Eligible if UP/Ucr >4 g/g after 3 months of RAS blockade & BP <130/75
- RX: ACTH escalating to 40u or 80u twice weekly, given for 90-180 days

Hladunewich et al., *Neph Dial Transplant*, Aug 2014
ACTH Treatment of iMN is associated with a decline in anti-PLA₂R

Membranous nephropathy treatment algorithm for patients with persistent nephrotic syndrome

1st line
- Calcineurin inhibitor
- Cyclophosphamide + steroids

2nd line
- Calcineurin inhibitor
- Cyclophosphamide + steroids

3rd line
- Rituximab
- ACTH

4th line
- ACTH
- Conservative therapy until RRT

eGFR > 60 ml/min/1.73m²

eGFR < 60 ml/min/1.73m²

Conservative therapy until RRT
The Future: ongoing trials in MN

- **MENTOR:** MEMbranous Nephropathy Trial Of Rituximab
  - Rituximab vs. Cyclosporine

- **CHART:** ACTH gel for resistant membranous
  - ACTHAR in 2 doses vs. placebo (1:1:1 allocation)

- **STARMEN:** Sequential therapy with TAcrolimus and Rituximab in Primary MEMbranous Nephropathy
  - Tacrolimus-Rituximab vs. Corticosteroids-Cyclophosphamide

- **MTAC:** MMF & TACrolimus vs. Tacrolimus
Thrombotic complications in MN

Adjusted risk of VTE by the level of serum albumin in 732 patients with available data

<table>
<thead>
<tr>
<th>Serum Albumin (g/dl)</th>
<th>N</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference range ≥3.0</td>
<td>219</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8 to &lt;3.0</td>
<td>66</td>
<td>1.41</td>
<td>0.34, 5.87</td>
<td>0.64</td>
</tr>
<tr>
<td>2.6 to &lt;2.8</td>
<td>74</td>
<td>2.17</td>
<td>0.63, 7.46</td>
<td>0.22</td>
</tr>
<tr>
<td>2.4 to &lt;2.6</td>
<td>72</td>
<td>2.05</td>
<td>0.59, 7.12</td>
<td>0.26</td>
</tr>
<tr>
<td>2.2 to &lt;2.4</td>
<td>77</td>
<td>1.31</td>
<td>0.31, 5.62</td>
<td>0.72</td>
</tr>
<tr>
<td>2.0 to &lt;2.2</td>
<td>82</td>
<td>4.32</td>
<td>1.46, 12.77</td>
<td>0.01</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>142</td>
<td>3.56</td>
<td>1.28, 9.88</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;2.8 versus ≥2.8</td>
<td>447/285</td>
<td>2.53</td>
<td>1.17, 5.47</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Lionaki S et al. CJASN 2012;7:43-51
Prophylactic anticoagulation?

- Markov decision model to predict benefit-to-risk ratios of prophylactic anticoagulation (benefit of VTE risk prevention relative to major bleed risk increase) in patients with MN
- Benefit-to-risk ratio mostly favorable if bleeding risk low; much less favorable if bleeding risk intermediate or high

<table>
<thead>
<tr>
<th>Level of serum albumin (g/dl)</th>
<th>Low Benefit-to-risk ratio</th>
<th>Intermediate Benefit-to-risk ratio</th>
<th>High Benefit-to-risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>4.5 (378/84)</td>
<td>1.3 (378/286)</td>
<td>0.6 (377/614)</td>
</tr>
<tr>
<td>&lt;2.8</td>
<td>5.2 (437/84)</td>
<td>1.5 (436/286)</td>
<td>0.7 (436/614)</td>
</tr>
<tr>
<td>&lt;2.5</td>
<td>7.7 (650/84)</td>
<td>2.3 (649/286)</td>
<td>1.1 (648/614)</td>
</tr>
<tr>
<td>&lt;2.3</td>
<td>10.0 (842/84)</td>
<td>2.9 (841/286)</td>
<td>1.4 (840/614)</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>13.1 (1103/84)</td>
<td>3.9 (1103/286)</td>
<td>1.8 (1102/614)</td>
</tr>
</tbody>
</table>
Welcome to GNTools.com
A tool to decide about prophylactic anticoagulation for membranous nephropathy

Our tool is based on a decision analysis weighing the benefits (thrombosis prevention) and risks (major bleed) of prophylactic warfarin anticoagulation. It is specific for patients with membranous nephropathy with no other risk factors for clot.
Open questions:

Biology:
• What other antigens account for the remaining ~20% of “idiopathic” MN? What about tumor antigens?
• What additional “hits” cause a genetically at-risk individual to develop overt disease?

Diagnosis:
• Can anti-PLA2R levels—with or without genetics—be specific enough to offer diagnosis without kidney biopsy?

Treatment:
• Should anti-PLA2R levels dictate treatment escalation/de-escalation BEFORE a change in proteinuria or GFR occurs?
• Does lack of response of anti-PLA2R levels indicate a need for different or more aggressive immunosuppression?
• How might the newer anticoagulants (factor Xa and thrombin inhibitors) change our prophylactic anticoagulation strategy in at-risk nephrotic patients?
Conclusions:

- Progress over the past decade has dramatically enhanced our understanding of MN pathobiology
- Expect discovery of new membranous antigens and deeper understanding of how they drive podocyte injury, complement activation, etc.
- Expect a shift in nomenclature to more immunologically accurate terms than “primary” and “secondary” (e.g. Anti-PLA2R membranous nephropathy, etc.)
- Genetic and biomarker testing (e.g. autoantibodies) may become commonplace for diagnosis, risk stratification and to guide treatment decisions (e.g. a “membranous nephropathy diagnosis panel.”)
- Ongoing efforts to improve therapy, with strategies that may include targeting B cells & antibody production (rituximab, belimumab, bortezomib), removing or adsorption of pathogenic antibodies, and manipulating complement activation